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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,901	02/02/2006	Mark Ashton	BJS-620-401	1869

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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
05/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/556,901	ASHTON ET AL.	
	Examiner	Art Unit	
	NIZAL S. CHANDRAKUMAR	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,11,12,31,34,37-39 and 44-48* is/are pending in the application.

4a) Of the above claim(s) *1-4,6-9,11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,34,37-39,44-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/21/2008 has been entered.

Status of the claims:

Claims 1-4 withdrawn

Claim 6-9 withdrawn

Claims 11-12 withdrawn

Claim 5 cancelled

Claim 10 cancelled

Claim 13-30 cancelled

Claim 32-33 cancelled

Claim 35-36 cancelled

Claim 40-43 cancelled

Claim 49-50 cancelled

Claims 31, 34, 37-39, 44-48 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 34 and dependent claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 recites 'solvate or chemically protected form thereof'. What are the structures of these compounds? Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claims. *For example*, solvated compound should have a defined, definite chemical composition (such as monohydrate, 0.75 CH3OH etc.). The definition of these terms in the specification is also vague and indefinite.

Claim also recites C5-6 arylene. It is unclear what is the structure of a C5-arylene is?

As stated in *In re Zletz*, 13 USPQ2d 1320, 1322, "An essential purpose of patent examination is to fashion claims that are precise, clear, correct and unambiguous."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 34, 37-39, 44-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making four (two are esters and, two are acids corresponding to the esters) of the compounds of the claims, does not reasonably provide enablement for making the wide variety of compounds encompassed by the formula I. The formula I is also drawn to unknown solvates and to compounds of undisclosed structures. The biological activity reported for the compounds and there supposed prodrugs is, at best, inconsistent (see below). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims are drawn to substitutions layered on top

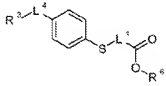
of substitutions and attempts to address the feasibility issues relating to each one of the these billion possibilities would require undue burden on the Examiner. For this reason only examples were provided in this office action to illustrate lack of enablement in the specification. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)).
1) The breadth of the claims, 2) The nature of the invention, 3) The state of the prior art, 4) The level of one of ordinary skill, 5) The level of predictability in the art, 6) The amount of direction provided by the inventor, 7) The existence of working examples, 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

While all the above factors were considered, some of the specific considerations are described below:

The nature of the invention: This invention relates to hydroxamic acid compounds and compositions containing the compounds, useful to treat various conditions alleviated by the inhibition of glyoxalase I.

The breadth of the claims: The claims are drawn to compounds of the Formula I



wherein L1 and L4 are

L^1 is optionally substituted [[C_{1-4} alkylene,]] C_{5-6} arylene, C_{1-4} alkylene-C_{5-6} arylene or $-L^5N(R^5)L^6-$, or C_{1-3} alkylene substituted by either C_{1-7} alkyl or C_{5-7} aryl, wherein L^5 and L^6 are independently selected from optionally substituted C_{1-4} alkylene and C_{5-6} arylene, and R^5 is H or C_{1-4} alkyl;
$-L^8YN(OH)C(=O)L^{10}-$ and $-L^9C(=O)N(OH)YL^{10}-$, wherein L^9 and L^{10} are independently selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene-C_{5-6} arylene and a single bond, wherein Y is NH or a single bond;

Thus Formula I is drawn to substituents layered on top of substituents that vary independently and lead to compounds of a wide variety of structures. These compounds encompass molecules that widely vary in the physical and chemical properties such as size, molecular weight, logP, acidity and basicity, properties that are known in the art to greatly influence the PK and PD parameters, not to mention the ability to productively bind to claimed biological target molecules. In addition, the claims are drawn to undisclosed solvates and 'chemically protected' derivatives of formula making the number of theoretically conceivable compounds wide, rendering the scope of the claims large, one that is not supported by the disclosure in the specification.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The amount of direction or guidance present: Three of the five generic, speculative, synthetic schemes present in the specification pertain to the making of the compounds. There are 7 working examples in the specification of which 4 are relevant to the elected group. All of these 4 working examples (i.e. 4 compounds) are prepared from the same aryl-mercapton, i.e. 4-mercaptobenzyl alcohol. Thus the amount of direction present in the specification enable making compounds is extremely limited in scope.

This procedure involving the displacement reaction by the nitrogen of the hydroxamic acid nitrogen for making L4 -CH2- is unavailable for making L4 -arylene variable.

Although the explicit statement to include -C=ON(OH) anywhere in the molecule is deleted in the amended claims, the claim limitations nevertheless, in effect, imply a most important limitation of the claims, that hydroxamic acid group is present, some where in the molecule. Such extremely broad generalizations are in contradiction with the basis of quantitative structure-activity-relationship (QSAR). The specification provides guidance for introducing this group with *one* example. i.e. by nucleophilic displacement at a benzylic situation.

There is complete lack of direction or guidance for procuring the crucial starting materials, i.e., the aryl mercaptons needed for making the compounds of the formula I. Very few known aryl-mercaptons are amenable to the preparation of the billion possible L4-R3 variations. The specification does not provide reference to commercial source or literature citations of procedures for obtaining the starting materials. Table -4 which mentions commercial sources but provides for no compound relevant to the instant claims. In lieu of guidance, the specification cites the generic teachings of organic chemistry text books such as, Green's Protective Groups in Organic Chemistry (see page 32 of the specification).

The specification does not provide direction for making solvates of the compounds of formula I.

The presence or absence of working examples. The working examples present in the specification are extremely limited. There are four working examples for making the compounds (see below for use related working examples) all of which related to a single set of variables as per the elected group (see above). Of these, two are methyl and ethyl esters of the two acids. The specification claims that these esters may be prodrugs of the acids since they are hydrolyzed in cell assays. Thus, in effect, the working examples teach *two* compounds of the *billions* of possibilities for the formula I, both compounds with the same variables R1 = H, L3 = single bond, R3 = H, L4 = CH2, R4 = H.

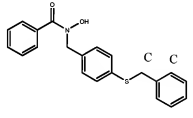
There is one example in the specification for introducing the mandatory hydroxamic acid functionality (see above). Scheme-5 in page 42, of the specification speculates on a way to introduce R4 aryl or R4 heterocyclic group by Suzuki coupling methods. There are no working examples wherein this

chemistry is demonstrated.

There are no working examples of solvates of the compounds of the formula I.

The disclosed examples (four compounds) in Table 1 (of page 47) conform to this stated preferred variables. The biological activities for these 'preferred' combination of variables are given in Table 2 and 3 (pages 56 and 57). Of the 4 compounds tested two had IC50s of 2 and 10 micromolar (deemed 'low IC50 values') and the inactive two compounds (esters) were deemed to be active in the cell proliferation assay (IC50s 8 and 15 micromolar). Surprisingly compound E deemed active in the in vitro assay (Table 2) is inactive in the cell proliferation assay (Table 3). The later result is indicative of the unpredictability in the art of biological chemistry.

The only two working examples present in the specification correspond to the following,



wherein C represents carboxylic acid groups corresponding to the two compounds. The only difference between the two compounds is the positioning of the same (carboxylic) group which would place these groups in very similar position in space relative to the macromolecular target. In spite of this very close structural similarity, the compounds show inconsistent ex vivo activity. See Table 3, compound A is not even present in Table 3.

The quantity of experimentation needed: Based on: a) the structures of the two disclosed compounds thus lacking QSAR, b) claims to widely varying structures encompassed by the formula (I), c) lack of disclosure with respect to what is needed for inhibitory interaction with glyoxalase (i.e. pharmacaphore), and d) applicant's characterization of what is considered 'biologically active' , one of ordinary skill in the art would be presented with an unpredictable amount of research effort to identify a compound out of the plethora of possibilities encompassed by the formula I that would have useful biological properties.

The instant claims consists of subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "*a patent is not a hunting license.* It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claims 31, 34, 37-39, 44-48 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625